

Management of Noncommunicable Diseases Department
Chronic Respiratory Diseases and Arthritis

Prevention of Allergy and Asthma Interim Report

Based on the WHO/IAACI Meeting on the
Primary Prevention of Allergy and Asthma

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Introduction

S G O Johansson

This Interim Report is a short consultative document produced from a collaborative project between the International Association of Allergology and Clinical Immunology-World Allergy Organisation (IAACI-WAO) and the World Health Organisation (WHO). The Interim Report is the forerunner of the final document "Prevention of Allergy and Asthma", which will take the form of a WHO Technical Report.

Background

The prevalence of asthma and allergy is increasing. It is estimated that over 40% of the world population is atopic. Asthma occurs in around 10-15% in the paediatric population and is estimated to affect between 100 and 150 million people worldwide, placing an enormous strain on health resources in many countries. Asthma is a major cause of hospitalisations for chronic diseases in children in the western world.

A strategy is needed to prevent this increased prevalence of allergy, which is a major cause of asthma (often labelled as a "non-infectious epidemic"). Over 2 years ago IAACI recognised the need for a global organisation taking responsibility for exchange of science and education in allergy. The name of the Association will be changed to World Allergy Organisation (WAO) after the IAACI Congress in Sydney in October 2000. Since chronic respiratory disease (including asthma) will be one of four major noncommunicable diseases of immediate focus for WHO, WHO invited IAACI-WAO to participate in this collaborative project.

WHO/IAACI-WAO created a working group consisting of six "Chapter Chairpersons", each with co-authors and a meeting of the group took place on 5 and 6 December 1999 in WHO headquarters in Geneva. A list of participants is attached.

Aims and Objectives

The aim of the joint WHO/IAACI-WAO project is to first produce an evidence-based, expert-approved master document which will take the form of a WHO Technical Report entitled "Prevention of Allergy and Asthma". From this, various strategic guidelines will be developed that are targeted towards governments, health care professionals, lay organizations, and patients.

Scope

The proposed title of the document was "Primary

Prevention of Allergy and Asthma", however, it was recognised that primary prevention of asthma may often be secondary prevention of allergy, and the title was changed to reflect this.

However, in the main, the document will focus on primary prevention, with respect to allergy. Tertiary prevention (ie treatment of the disease) will not be addressed, as this is adequately covered elsewhere (eg GINA – Global Initiative for Asthma, January 1995). The final document will contain a glossary of all terms used.

Definitions

Hypersensitivity: if an individual reacts to something in his environment to which others do not.

Allergy: if the hypersensitivity is mediated by immunological mechanisms.

Atopy: if the allergy is IgE mediated:

In terms of prevention:

Primary: prevention of immunological sensitisation (ie the appearance of IgE).

Secondary: preventing the development of an allergic disease following sensitisation (and especially development into severe diseases such as asthma).

Tertiary: treatment of asthma and allergic diseases.

Asthma (as defined by GINA): Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils and T lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. This inflammation also causes an associated increase in airway responsiveness to a variety of stimuli.

Non-Atopic Asthma: There appear to be two "arms" to asthma: allergic and non-allergic. Much information is available on the former (both genetic and environmental). Little is known about the genetic basis for non-allergic asthma, though some data are available on environmental factors (smoking is of primary importance; viral infection, exercise, chronic sinusitis and gastro-oesophageal reflux may all be relevant). Non-atopic asthma is included within this report since it may constitute around 50% of adult asthma and is often severe. Although the aetiology is less well defined, similar inflammation is present in the lungs of non-atopics and atopics and the same drugs treat both diseases.

Format and Structure

The Master Document, to be completed later, will adopt the same format as the six chapters in this Interim Report, with supporting references added. Further,

while the current document lists recommendations for further research at the end of each chapter, these recommendations will be combined into a single chapter in the Master Document.

1. Chapter 1: Genetic and Environmental Influences

Innes Asher, Elif Dagli, Stephen T Holgate

1.1. Introduction

Genetic predisposition and environmental factors influence the development of allergic rhinitis, atopic eczema and asthma. There is clustering of these diseases in families, and genetic differences may account for part of the wide inter-country differences in prevalence. However environmental influences are also crucial to the expression of these diseases, because of wide variation in prevalence found in people of similar genetic stock. The concept of gene-environment interaction may be considered as the basis for allergic disease.

1.2. Genetics of atopy

1.2.1. Definition of the atopic phenotype

Over recent years, considerable amounts of data have become available on the genetic background to asthma and other allergic diseases. These data have been derived from studies on twins, from parental history, from other genetic studies of atopic diseases and from genetic studies of non-atopic asthma (Aspirin induced asthma, certain types of occupational asthma, etc).

By careful review of these data, it is now possible to provide practical, useful, genetic information for physicians, patients and families.

Evaluation of partial phenotypes, polychotomies and the use of scores have also contributed to the increased understanding of the role of genetics in allergic disease. There is now extensive support for the concept that Th-2 drives expression of IgE and atopy: there is also increasing evidence that such traits are inherited.

A review of the literature indicates that it is possible to determine the risk of an individual becoming atopic. A number of factors appear to be involved. Offspring born to an atopic mother have a high risk of becoming atopic. Those born to an atopic father are at less risk, though the risk is still high. When both parents are atopic, the risk of an offspring becoming atopic is extremely high. The risk associated with atopic siblings or grandparents remains to be determined.

As data on the genetics of atopy increase it will be possible to provide genetic counselling to putative parents.

1.2.2. Molecular regulation of atopy. Many different genes are involved in the genetic predisposition that drives a systemic or allergic local tissue response. A number of genes, including the IL-4 cluster on chromosome 5q31-33, are involved in triggering the molecular pathways that initiate Th-2 polarisation and the down stream consequences of this. Cytokines such as SCF, TNF α , TGF β play an important role, as does dendritic cell-T cell signalling.

T cell-B cell signalling requiring antigen processing and presentation (including MHC Class II) and the involvement of co-stimulatory molecules, also plays a key role.

There are new data on the role of cell adhesion molecules (eg VCAM-1) and chemokines.

1.2.3. Whole genome searches. Whilst there are some constraints on methodology, whole genome searches have been used to identify candidate regions and candidate genes.

1.2.4. Candidate Gene and Association Studies. There is a focus on IL-4 and IL-13 (Chr 5q) and their polymorphic receptors (Chr 16 and Chr X). These cytokines interact both with formed elements (eg epithelial cells and fibroblasts) as well as with Th cells and B cells. Other candidate genes such as HLA, TNF α , (Chr 6), chemokines and their receptors, Fc ϵ R1, (Chr 11q), mast cell chymase, enzymes of leukotriene-generating pathway and the β_2 -adrenoceptor have been identified.

1.2.5. Atopic versus non-atopic gene studies. Data from gene studies on atopic versus non-atopic asthma may assist in the identification of candidate genes that are involved in the allergic process.

1.2.6. Gene-environment Interaction. There are three main areas in which gene-environment interaction has been studied:

The antigen-processing role of HLA (eg pollenosis and occupational asthma),

The maternal influence on atopic phenotype – genetic or early (intrauterine or perinatal) environment,

The genetics of mucosal immune response in the context of organ development eg epithelial-mesenchymal trophic unit, passive cigarette smoke exposure, other pollutants and diet.

1.3. Environmental influences

Environmental influences may be divided into two categories: protective and causative.

1.3.1. Protective environmental influences include:

- diet, (especially oily fish, vegetables, fruit, antioxidants, adequate maternal diet in pregnancy, breast feeding)
- microbial exposure (including intestinal microflora and farm animals)
- large family size
- socio-economic factors (access to medical care/advice)
- infection (including TB and early childhood respiratory infection)

1.3.2. Causative environmental influences include:

- environmental tobacco smoke (prenatally, in infancy and childhood), and active smoking in children and young people
- socio-economic factors (affluent life-style: well insulated, centrally heated homes etc)
- diet (especially *trans* fatty acids margarine, maternal diet in pregnancy)
- allergen exposure (house dust mite, cockroach, cat, dog, rat, mice, foods etc)

- moulds
- damp housing
- traffic pollution (eg diesel particulates, SO₂, NO_x)
- occupational exposure
- small family size

1.3.3. Other environmental influences and potential interactions. The role of other potential environmental influences including immunisation, exercise, and climate (eg massive pollen release following thunderstorms) are under investigation, as is the role of potential interactions between environmental influences.

1.3.4. Timing of environmental influences. The timing of environmental exposures is critical. Thus, the effects of *in utero* exposure and exposures in early and late childhood and adult life play an important role in determining the nature of the development of the allergic response.

1.4. Recommendations for further research

Once the human genome has been decoded, it is of critical importance to take full advantage of this to identify susceptibility genes linked to disease phenotypes, for subsequent design of environmental and drug interventions.

Further studies connecting genetics to monitoring of the environment with regard to the natural history and severity of allergic rhinitis, atopic eczema and asthma would also create new opportunities for understanding disease mechanisms and factors that determine chronicity and severity.

2. Chapter 2: Early Immunological Influences

Patrick G Holt, Charles K Naspitz and John O Warner

2.1. Introduction

Once allergic disease is established, no treatments have convincingly been shown to modify the natural history of the disease. No cure has been identified for any allergic disorder and the atopic march from food allergy with atopic dermatitis through inhalant allergy with asthma and allergic rhinitis proceeds inexorably. Thus attention must obviously focus on the potential for prevention, but in the first instance, there must be a full understanding of the immunological events leading to sensitisation, and eventually disease, in order to identify appropriate therapeutic targets.

In the last decade, there has been a paradigm shift in

perception of how the allergen responder phenotype is determined. Previously it was felt that allergy resulted primarily from genetically determined immunological hyperresponsiveness amongst a small subset of the population in whom trivial non-pathogenic antigens triggered potent immune responses dominated by the production of IgE antibody. Non-allergic individuals were viewed as immunologically unresponsive to these agents as a result of efficient mucosal defences. However, more recently it has become clear that cognate immunity against environmental allergens is the norm in humans and it is the nature of the underlying cytokine responses within the allergen-specific T-helper memory

cell populations that determine the clinical responder phenotype. Based both on T-cell cloning experiments and short term bulk cultures of unmanipulated peripheral blood mononuclear cells, studies have confirmed both the universality and the reciprocal patterns of allergen specific Th-1 clones in non-atopics (with a dominant production of IFN- γ) and Th-2 polarisation of allergic individuals (with predominant production of IL-4, IL-5, IL-10 and IL-13). IL-4 and IL-13 are particularly critical in the gene deletional switching to IgE production. There is not complete polarisation of responses amongst atopic individuals but a significant Th-2 component in the response remains the defining feature of the atopic phenotype.

In the last few years, increasing evidence points to key events that determine the responder phenotype in adulthood that may have evolved in very early life. From epidemiological studies, it is clear that high level exposure to aeroallergens is strongly associated with allergic sensitisation in the first years of life. Sensitisation to aeroallergens such as house dust mite with high level exposure in early life is associated with an infinitely greater risk of having continuing asthma into adolescence. Chronic asthma with persisting symptoms and persistent bronchial hyperresponsiveness are associated with early sensitisation while later sensitisation has much less impact on persisting symptomatology and hyperresponsiveness. It has, for instance, been suggested that the risk of sensitised children developing airway hyperresponsiveness doubles with every doubling exposure to house dust mite.

2.2. Ontogeny of allergic response in the antenatal period

It is well established in murine models and to a lesser extent in the human situation that the foeto-placental unit produces Th-2 cytokines throughout pregnancy. These, in turn, inhibit maternal Th-2 activity, which would compromise continuation of the pregnancy. This inevitably creates a Th-2 biased intrauterine environment that has significant influences on the evolving foetal immune response as well as effecting maternal responses to foeto-paternal antigens. The foetus has T-lymphocytes in the thymus as early as week 9 of gestation. By 14 weeks, B-lymphocytes are seen in a range of organs including the lungs and gut and by 19–20 weeks, circulating B-cells have detectable surface IgM. This implies that the foetus is able to mount a full immunological response leading to the production of specific antibody by the middle of the second trimester of pregnancy.

It has recently been possible to demonstrate small quantities of allergen not only in the circulation of pregnant women but also in the amniotic fluid. This leads to direct exposure of the foetus either through the skin, the respiratory tract (because of foetal breathing

movement) and perhaps most importantly, the foetal gut, where there is a 70% turnover of amniotic fluid in 24 hours.

Peripheral blood mononuclear cells sensitised to common environmental allergens such as β -lactoglobulin of cow's milk, ovalbumin from egg and Der p1 from house dust mite, have been found as early as 22 weeks' gestation. Much evidence now points to this sensitising process occurring via the foetal gut where mature antigen presenting cells can be demonstrated from 11–12 weeks' gestation with T-lymphocytes and B-lymphocytes by 16 weeks' gestation.

Thus by birth, there is a universal Th-2 biased response to environmental allergens. Factors that increase this bias include maternal atopy that may be a consequence of genetic imprinting. However, it is rather more likely that the intrauterine environment is more allergy biasing where the mother, herself, is already atopic. Thus, there is both increased IL-10 and IgE in the amniotic fluid of atopic compared with non-atopic mothers. The latter in particular may facilitate low dose antigen focusing of the antigen presenting cells in foetal gut which have detectable low-affinity IgE receptors in significant quantities. Additional contributions may be made by maternal nutrition during pregnancy. Putative associations include maternal consumption of polyunsaturated fatty acids which will influence prostaglandin (PG) E₂ production which in turn has an effect on Th-2 allergy biased responses. It is also possible that the programmed velocity of foetal growth and, therefore, its overall nutrient demand may also have an impact on foetal nutrition in later pregnancy, therefore affecting susceptibility to Th-2 biased responsiveness.

While cigarette smoking in pregnancy clearly affects lung function and susceptibility to wheeze, evidence that it affects allergic sensitisation is less well documented, though there is evidence of a link from some studies.

2.3. Modulation of immune responses postnatally

At birth, there are some differences in the cytokine profiles released from either mitogen or allergen stimulated cord peripheral blood mononuclear cells from atopics compared with non-atopics. These differences occur despite an often enhanced proliferative response to allergen with lower IFN- γ and indeed also Th-2 cytokine production. What characterises the infant destined to be atopic is a persistence of the Th-2 biased response through infancy with increasing production of IL-4 and IL-13 and a continuing reduced production of IFN- γ .

Conversely the non-atopics develop increasing IFN- γ production and no increase, or a decrease, in Th-2 cytokines.

There is growing evidence that postnatal modulation

of T-helper cell responses occurs via bystander effects of cytokines generated during host immune responses against microbial organisms. This phenomenon fits very well with the hygiene hypothesis proposed as a consequence of epidemiological studies demonstrating a higher allergy risk in first born than those born subsequently in families, and lower risks in environments where higher frequency of respiratory infections occur. There have also been associations between lower allergy risk and measles or hepatitis A infection in early childhood. There are additional studies demonstrating a reciprocal relationship between tuberculin responsiveness and allergy, though there are also studies that show no relationship. Indeed it has been shown in animal studies, though less convincingly in humans, that BCG vaccination might promote Th-1 responsiveness. Perhaps the most potent source of immuno-stimulatory signals to effect a T-helper cell modulation is from enteric organisms including normal microbial flora as well as enteric pathogens. Although not fully confirmed, indirect evidence for this hypothesis comes from identification of different gastrointestinal flora in paediatric populations from high versus low atopy prevalence communities and from the link between frequent use of oral antibiotics and higher subsequent allergy.

2.4. Allergen exposure

The relationship between concentration of allergen exposure and atopy risk is complex. Limited evidence is accruing that high exposure of the mother, pre-conceptually and during pregnancy, is associated with a higher production of maternal IgG antibody. This, in turn, is not only inversely correlated with the level of cord peripheral blood mononuclear cell proliferative responses to allergen but also with a reduced subsequent sensitisation rate and atopic symptoms. This perhaps provides one indication of a potential therapeutic target. Although previous studies on hyposensitisation in pregnancy showed no effect, one observational study has shown that allergen immunotherapy administered to mothers through pregnancy, which in turn often induces high maternal IgG antibody, is associated with lower atopy in the offspring.

Postnatally, there is a great deal of evidence that would suggest that the higher the allergen exposure, the greater the risk of sensitisation and subsequent disease. Thus there are a number of trials that have shown that reduction of allergen exposure postnatally can have at least a transient effect in reducing allergic sensitisation and disease.

2.5. Prevention – potential options for early intervention

2.5.1. Antenatally (primary prophylaxis – before sensitisation)

Strategies to increase maternal production of IgG antibody to common environmental allergens, perhaps by high dose allergen exposure, may be of value. Optimisation of nutrition could avoid foetal nutritional compromise in late pregnancy and modulate PGE₂ production. Avoidance of antenatal smoking will reduce wheezing illness but not necessarily atopy.

2.5.2. Secondary prophylaxis (neonatal intervention after sensitisation but before development of disease)

Non-specific immuno-stimulation employing either mycobacterial vaccines, the use of oligonucleotide bacterial products with CpG motifs or dietary manipulation may enhance gastrointestinal colonisation with known benign immuno-stimulatory bacterial strains. Alternatively, immuno-prophylaxis might be employed by exposing infants to high doses of allergen eg intranasally to enhance the modulatory effect on T-helper responses. It may also be possible to consider the use of the new generation of Th-2 antagonist drugs now being developed.

2.5.3. Tertiary prophylaxis (interference with the atopic march after allergic sensitisation and the development of the first signs of disease)

Three studies have been performed using antihistamines (2 with ketotifen and 1 with cetirizine) which have suggested that these products can have a preventive effect on the development of asthma in infants with atopic dermatitis and allergic sensitisation or infants with evidence of sensitisation born to atopic families. Allergen immunotherapy has been shown to effect a Th-2 to Th-1 switch in response to allergen. Early employment of this therapeutic intervention has been shown to interrupt the expansion of allergic sensitisation from a single allergen to multiple allergens and is currently being tested in the context of interruption of progression from allergic rhinitis to asthma.

2.6. Recommendations for further research

Further studies are needed to investigate the role of the different gastrointestinal flora found in paediatric populations with high versus low atopy prevalence.

Similarly, investigation of the link between frequent use of oral antibiotics and higher subsequent allergy may suggest a potential intervention.

Studies designed to increase maternal production of IgG antibody, either by high dose allergen exposure of the mother pre-conceptually and during pregnancy, or by allergen immunotherapy administered through pregnancy, may be of value.

3. Chapter 3: Predictive and Early Diagnosis

Ulrich Wahn, Alexander Chuchalin and Marek L Kowalski

3.1. Introduction

Although predictive factors for allergy (rhinitis, atopic dermatitis and conjunctivitis) are presented, the primary focus of this chapter is on asthma.

The value of accurate predictive diagnosis is obvious given the enormous and increasing social and economic burden of asthma on a global scale. Furthermore, studies in asthma show that the longer the time between diagnosis and treatment, the greater the impairment to final lung function and this has tremendous implications from the public health point of view. Improvement in early diagnosis is important, to prevent lung function becoming abnormal, even though there are few evidence-based data available to support this contention.

In order to predict high-risk groups, it is essential to have screening tests, with validated markers, which are accurate, reliable and of known predictive value. This is the ideal situation: however, when data are incomplete, the predictive positive and negative value of tests is emphasised. Caution is exercised when making such recommendations, to ensure that no unfair commercial advantages ensue.

In the absence of reliable predictive markers for atopic disease, there are no general recommendations. Conversely, it is possible to make recommendations for specific groups based on specific markers. Once a child has atopic disease, the situation is different. Eczema in a baby or in young child is a good marker for asthma, and allergy to egg in the first year may be a good marker for respiratory allergy. Early intervention is obvious when patients are symptomatic, but asymptomatic high-risk groups may benefit from early diagnosis and identification. Again, if exact predictors are not available, current knowledge in terms of early signs, rather than symptoms of established asthma, is extremely important. Finally, if an intervention is made, it is essential to prove that it does make a difference.

3.2. Predictive diagnosis

Atopy is the best predictor for asthma in children and young adults. A number of factors appear to be involved in the development of allergy, including family history, family size, atopic status of the mother versus the father (mother seems more predictive), in-utero or neonatal factors (e.g. low birth-weight) and maternal cigarette smoking. The sensitivity, specificity and relevance of these predictive factors are discussed. Few hard data are available, but these factors have some support from epidemiological data and may be helpful to doctors, in terms of prevention of disease.

Factors that increase risk can also be used as predictors: bronchial hyperreactivity, sinusitis and wheeze are all risk factors for developing asthma. In early infancy wheeze (particularly persistent wheeze) and severe asthma attacks and (more importantly) repeated asthma attacks are identified as potential predictors for persistent asthma.

3.2.1. The important risk factors related to allergic sensitisation

Genetic background: Family history of atopy is a good positive predictor of the development of allergic sensitization in a child. Children with a positive family history of atopy in first-degree relatives have been shown to be at greater risk to become sensitised and develop clinical manifestations during the first decade of life. However for the whole population a prediction for atopy and asthma based on family history has rather limited value because the majority of children developing asthma during the first years of life come from a family background without any atopic manifestations.

The genes regulating IgE-production, specific sensitisation and the skin or airway manifestation of atopic disease are currently being investigated. A large number of chromosomal loci have been identified. Unfortunately so far, none of the loci is helpful in identifying children at risk. The risk to develop one of the atopic phenotypes (hay fever, atopic dermatitis asthma) is also to some extent influenced by the genetic background.

Atopic phenotype: The link of certain atopic phenotypes, which is characteristic for the natural development of atopic diseases, allows the detection of children at risk very early and provides a useful basis for early intervention measures aiming at secondary prevention.

During the first months and years of life a high percentage of atopic individuals will manifest atopic disease. In general, atopic dermatitis is the first manifestation. Children who develop atopic dermatitis early in infancy and have an additional positive family history for atopy are at high risk to develop asthma and other allergic airway manifestations during the subsequent years. On the other hand only about 10% to 20% of patients suffering from allergic rhinitis will develop asthma in the future.

Presence of specific IgE to allergens: The earliest IgE responses, which can be detected during infancy, are related to food proteins, particularly hen's egg and cow's milk proteins. Children with high IgE-responses to these food proteins have been shown to be at risk to develop sensitisation to indoor or outdoor aeroallergens some years later. Use of skin prick tests and immunoassays to identify such individuals may be of predictive value.

3.2.2. Immunological markers

Several immunological markers have been studied in order to identify their predictive capacity. Unfortunately, their predictive capacity for atopy is either low (eg total IgE, cord blood IgE and blood eosinophilia) or not sufficiently well documented (eg specific IgG to foods, decreased interferon-gamma and IL-12 production by PBL).

Elevated cord blood IgE levels and eosinophil markers must be considered as risk factors for some form of atopic disease (eg atopic dermatitis), however, they are inadequate for the identification of children at risk and for the prediction of the disease.

Blood eosinophilia and the presence of specific IgE with a diagnosis of atopy may be considered a good predictor, and the presence of IgE to an inhalant allergen is predictive of future inhalant allergy.

3.2.3. Predictive factors for asthma, non-related to allergy

With the possible exception of family history, there is no way to predict non-atopics who will develop asthma later in life, and hence there is no means of primary prevention. A number of factors have been implicated including a history of RSV infections in childhood, chronic rhinosinusitis, non-allergic rhinitis with eosinophilia (NARES), maternal smoking, gastro-oesophageal reflux, and severe or repeated asthma attacks in childhood, but further work is required before these factors could be considered as predictive.

On the other hand, genetic loci associated with bronchial hyperresponsiveness and asthma but unrelated to atopy have been identified on chromosomes 5 and 6 raising the possibility of future prediction of genetic risk of asthma independent from allergy.

3.3. Early diagnosis

Early diagnosis should lead to early implementation of proper treatment of asthma and thus to potential prevention of persistence and/or reduction of severity.

3.3.1. Early diagnosis based on symptoms and lung function

Proper interpretation of early symptoms: Cough and wheezing in infancy may have some predictive value for development and persistence of allergy and (particularly wheezing) for the development of later asthma. However, many children wheeze but do not become asthmatic. It may be possible to detect individuals at risk, since it has been shown that children who go on to suffer persistent wheezing have high levels of serum IgE at nine months.

Assessment of lung function and airway function variability: Lung function is a poor and rather late predictor for development of asthma since many patients at the early stage of the disease have normal

lung function. Although some children with normal lung function may have increased bronchial hyperreactivity (BHR), the significance of isolated BHR is not clear. Nevertheless the measurement of the airway function, airway variability and bronchial hyperreactivity is helpful for the diagnosis of asthma and in the future may be useful for identification of children at risk to develop asthma.

3.3.2. Diagnostic value of measurement of inflammatory markers

Currently, only lung function and not inflammation is measured. More studies of the possible predictive role of inflammation are needed, and a number of potential markers such as sputum eosinophilia and nitric oxide levels have been identified and may be relevant as potential predictors. The optimum would be lung function measurements plus improvements in the ways in which inflammation is measured.

3.4. Conclusions

In the absence of good clinical, immunological or molecular genetic predictors for atopy, primary prevention measures should only be introduced if they meet the following criteria. They should be of advantage to all and thus be recommended on a population level, they should be of no known harm to anyone and should not involve unreasonable costs.

In contrast strategies aimed at secondary prevention can be based on the early manifestation of atopic disease which usually occurs during infancy. Potential interventions include avoidance measures, measures to induce tolerance, early pharmacotherapy and early immunotherapy.

3.5. Recommendations

3.5.1. Environmental factors

Clarification of the role of lifestyle factors including the early exposure to allergens (eg pet ownership) versus protective environmental factors (eg infections) may help to identify high-risk population groups.

3.5.2. Cumulative risk from the presence of several risk factors

Population studies should allow assessment of the predictive value of cumulative risk associated with the presence of several risk factors (eg environmental factors, plus new genetic markers or newly identified risk factors).

3.5.3. Immunological markers

Further work is needed to assess the predictive value (both positive and negative) of known and new immunological markers (eg specific IgG to foods,

decreased interferon-gamma and IL-12 production by PBL). Factors responsible for ineffective mechanisms of immune deviation, which do not allow efficient redirection of foetally determined Th-2 responses towards the Th-1 cytokine phenotype, should be also identified.

3.5.4. Identification and assessment of the risk factors for non-atopic asthma

Further study, possibly by follow-up of hypothesis-generating epidemiological studies is required in order to

identify risk factors which may be predictive for the development of non-atopic asthma.

3.5.5. Non-invasive methods for the detection of airway inflammation

More studies of the possible predictive role of inflammation are needed. These should be accompanied by the identification and validation of markers of inflammation, obtained by simple and effective non-invasive techniques.

4. Chapter 4: Preventive Measures

Arne Høst, Attilio Boner and Joseph Odhiambo

Co-author: Adnan Custovic

4.1. Introduction

In infancy the main atopic symptoms are atopic dermatitis, gastrointestinal symptoms, and recurrent wheezing, whereas bronchial asthma and allergic rhinoconjunctivitis are the main problems later in childhood. Adverse reactions to foods, mainly cow's milk protein, are most common in the first years of life, whereas allergy to inhalant allergens mostly occurs later. Correspondingly, specific IgE antibodies against milk and egg are most frequent during the first 2-3 years of life, whereas specific IgE against inhalant allergens is predominant later in childhood. It is very important to take into consideration the natural course of the disease when evaluating the results from interventional studies on prevention of allergic diseases.

4.2. Possible strategies in individuals at high risk and in the general population

It is well documented that atopic heredity is associated with an increased risk of the development of allergic diseases. However, the majority of children who develop atopic disease, particularly recurrent wheezing and asthma during early childhood, do not belong to high-risk groups (at least one first relative with doctor-diagnosed atopic disease) for development of atopic disease. Thus, some preventive measures may be beneficial in the general population and supplementary measures may be beneficial and recommendable only for high-risk individuals.

4.3. Methodology in preventive studies

When evaluating possible risk factors for the development of allergic diseases and the possible effect of preventive measures, several factors have to be taken

into account. The study design of both non-interventional and interventional studies should be prospective (true), including accepted well-defined diagnostic criteria/outcome measures, a sufficient duration of follow-up, and a proper sample size for adequate statistical evaluation. Furthermore, interventional studies should include proper randomisation, double blinding and a control for confounders, as well as proper registration of compliance and follow-up of dropouts. Due to recall bias and selection bias, retrospective studies should not be used for evaluation of predictive/risk factors. Similarly, cross-sectional studies are not suitable for assessment of cause-effect relationships between exposure to allergens/adjuvant factors and development of allergic diseases. In general, prospective non-interventional studies can be used to generate hypotheses on the relationship between cause and effect in development of allergic diseases: however, proper confirmation of a possible cause-effect relationship requires demonstration of the causative mechanism and effect of elimination/prevention of the suspected causative factors.

4.4. Evidence based recommendations

4.4.1. Infants without a special risk for allergic disease

From prospective non-interventional studies, breast-feeding has been associated with a lower risk of atopic dermatitis and food allergy as well as a lower risk of recurrent wheezing/asthma. Whether breast-feeding helps prevent allergy remains controversial due to the lack of evidence in some studies and because infants cannot, ethically, be randomly assigned to breast-feeding or formula feeding to enable a definitive study. However, common factors in studies reporting a benefit of breast-feeding are, firstly, prolonged breast-feeding (≥ 4 -6 months) and secondly, late solid food introduc-

tion (after 4 months). Introduction of complementary (solid) foods before 4 months of age has been associated with a higher risk of atopic dermatitis in prospective non-interventional studies. There is no evidence of a preventive effect of special diet during pregnancy or for the lactating mother.

Several longitudinal studies have shown a significant association between parental (particularly maternal) tobacco smoking and increased wheezing and asthma in children. This association is strongest up to 6 years of age. The severity and frequency of symptoms were found to be related to the extent of exposure in the home. Passive smoking has been associated with sensitisation to indoor allergens in some studies, but not in others. Importantly, maternal smoking during pregnancy is significantly associated with reduced respiratory function in early infancy and recurrent wheezing during infancy and early childhood.

There is evidence of a cause-effect relationship between exposure to indoor (chemical vapours, gases, formaldehyde and volatile organic compounds) and outdoor pollution and induction of respiratory symptoms in individuals with established disease. However, the possible role of pollutants in the development of asthma and atopic airway disease seems less important and needs further elucidation.

4.4.2. Infants with a high risk of allergic disease

Around 35% of neonates ("high-risk") have at least one parent or older sibling with previous or current doctor-diagnosed atopic disease. Several prospective studies have shown a preventive effect of extensively hydrolysed formulas in combination with avoidance of cow's milk proteins and solid foods during ≥ 4 months in high-risk infants on the cumulative incidence of atopic dermatitis and food allergy (especially cow's milk allergy) until the age of 4–7 years. Thus, a real prevention and not only a postponement of the onset of the disease has been documented. An effect of dietary allergy prevention has been demonstrated only in high-risk infants and not in non-high-risk infants. At present clinical trials are ongoing comparing the relative preventive effects of products with highly reduced allergenicity (extensively hydrolysed) with those formulas with moderately reduced allergenicity (partially hydrolysed): preliminary data indicate a greater effect with extensively hydrolysed formula. There is no evidence that soy formulas or other formulas based on whole proteins other than cow's milk protein are less allergenic than cow's milk based formulas. Thus, if exclusive breast-feeding for 4–6 months is not possible in high-risk infants, a documented hypoallergenic formula and avoidance of solid foods are recommended for the first four months of life. There is no conclusive evidence for a protective effect of a maternal exclusion diet neither during pregnancy nor during lactation.

The effect of exposure to tobacco smoke and to indoor allergens seems to be most pronounced for exposure during the first months/year of life, particularly in children with atopic predisposition. There seems to be a synergistic effect of several co-existing environmental factors. Whilst there is no direct evidence for the increase in allergen exposure, the indirect evidence is overwhelming. Most people with so-called "Western life-style" spend more than 95% of their time indoors and children spend more time indoors than ever before. The indoor environment of homes (introduction of central heating, wall-to-wall carpeting etc) has changed over the last 3 decades, making it more suitable for dust mite population growth. The number of indoor pets has increased, resulting in increased community exposure. Houses have become better insulated, with lower air-exchange rates, and a consequent substantial increase in concentration of potentially harmful substances in indoor air (allergens, air pollutants etc).

Airway hyperresponsiveness in children is mostly associated with airway inflammation due to allergic sensitisation. Chronic asthma is mainly associated with sensitisation to indoor allergens (house dust mites, animal dander etc) which are more important than the outdoor allergens, probably because of time spent indoors. Several studies have demonstrated a relationship (in a dose-dependent manner) between exposure and sensitisation, as well as a clear association between sensitisation and development of asthma. Also, a dose-response relationship between exposure to house-dust mites and development and severity of asthma has been demonstrated. Other longitudinal studies have shown that sensitisation to house-dust mites and animal dander antedates, and is a risk factor for, development of asthma in children. Epidemiological studies suggest that in areas with low levels of allergens in homes, the prevalence of sensitisation is low. So far, only one prospective, randomised study has investigated the efficacy of avoidance of indoor allergens (house dust mites) in high-risk infants followed from birth until the age of 4 years (Isle Wight of Study). This study has produced the first indication that a reduction in house dust mite allergen levels in the homes of such infants may reduce the prevalence of sensitisation to mites and recurrent wheezing during the first years of life. Recently, a prospective study has documented that mite avoidance measures can achieve and maintain a low mite allergen environment during pregnancy and in the first year of life in homes of infants at risk of atopy. Thus, in homes of high-risk infants, current evidence supports measures to reduce the level of indoor allergens, such as house dust mites and pets. Furthermore, as for non-high-risk infants, exposure to tobacco smoke, damp housing conditions and indoor pollutants should be avoided.

4.4.3. Children with allergic symptoms (secondary prevention)

Avoiding exposure to relevant allergens is a logical way to treat allergic diseases (eg allergic asthma) when the offending allergen can be identified and effective avoidance is feasible. Several controlled randomised studies have shown that allergen (especially house dust mite and animal dander) avoidance measures are effective both in reducing the level of allergens and in improvement of disease control. Specific immunotherapy has been demonstrated in many studies to be an effective treatment for patients with allergic rhinoconjunctivitis. Recently, specific immunotherapy with subcutaneous injections has been shown to be effective in allergic asthma in randomised controlled trials with extracts of house dust mites, pollen, and animal dander (especially cat). A significant reduction in asthma symptoms and medication, and a reduction in both non-specific as well as allergen-specific airway hyperresponsiveness has been documented.

4.4.4. Pharmacological intervention in infants/children with atopic dermatitis

A few studies of pharmacological (eg ketotifen, cetirizine) intervention in young infants with atopic dermatitis have reported a significant reduction in development of asthma. In one of these studies, this effect was documented only in a subgroup of children sensitised to grass pollen or house dust mites.

4.4.5. Other measures (avoidance of irritants, especially tobacco smoke)

The association between parental smoking and recurrent wheezing and asthma in children is well documented, with severity and frequency of symptoms related to the extent of exposure. Avoidance of passive smoking reduces morbidity and use of medication and improves lung function in asthmatics. Tobacco smoke appears to be one of the most important preventable asthma inducers and triggers. Others are gases (eg nitrogen oxides), chemical vapours, formaldehyde and volatile organic compounds.

4.5. Implementation of preventive measures

As direct evidence of the primary risk factors leading to the increase in asthma prevalence is lacking, it is necessary to test the hypothesis of changing the exposure to the risk factors for which there is a good evidence of an association with asthma. Evidence for risk factors with a direct causal role is most complete for indoor allergens (particularly house dust mites). Preventive measures have been appropriate for use in a public health intervention. More focused and specialised intervention strategies may be appropriate for those at high risk, whilst general health promotion may address

the needs of the general population. Since genetics and environment differ in different parts of the world, prevention measures may differ between affluent and non-affluent groups.

4.6. Evidence based recommendations

4.6.1. Infants without a special risk for allergic diseases:

- No special diet for the lactating mother
- If breast milk is not sufficient during the first 3-4 days, water is recommended
- Exclusively breast feeding for at least 4 months: if supplement is needed, conventional cow's milk based formula is recommended
- Avoidance of solid foods until 4 months of age
- Avoidance of exposure to tobacco smoke (also during pregnancy)

4.6.2. Infants with a high risk for allergic disease:

- No special diet for the lactating mother
- If breast milk is not sufficient during the first 3-4 days, water is recommended
- Exclusively breast feeding for at least 4 months: if supplement is needed, documented hypoallergenic formula is recommended
- Avoidance of solid foods until 4 months of age
- Environmental measures:
 - avoidance of tobacco smoke (also during pregnancy)
 - reduce allergen exposure early in life (house dust mites, furred pets, cockroaches)
 - avoid damp housing conditions
 - avoidance of pollutants

4.7. Further research recommendations

- Results from randomised prospective studies of primary prevention of asthma and allergies (awaited from UK, the Netherlands, Canada, Australia, and Denmark)
- Adequately powered, randomised, controlled studies to investigate the potential benefit of low-allergen domestic environments in patients with allergic disease. Such studies also should address compliance, cost-effectiveness, and be of adequate length (eg 12 months) and tailored for different socio-economic and age groups
- A large-scale trial on the wide-spread applicability of mite-allergen avoidance and the effect on patient symptoms, exacerbation rates, use of medication and overall health costs (one such study is currently being carried out in the UK)
- Prospective studies on the possible role of dietary factors in the development of asthma and allergy (eg salt intake, antioxidants, n3/n6 fatty acids etc)

- Prospective studies on the possible role of vaccinations and intestinal microbial flora on the development of asthma and allergy
- The possible role of human milk constituents (eg n3/n6 fatty acids, levels of alpha-linolenic acid, cytokines, etc) in long term prospective studies
- The role of outdoor and indoor pollutants on the development of asthma and allergy in long-term prospective studies

The role of viral infections on the development of asthma and allergy (although viral respiratory infections frequently trigger acute exacerbations of asthma, the relationship between such infections and asthma is not clear. There is some evidence supporting two different but not mutually exclusive hypotheses: “predisposed children are susceptible to asthma and respiratory tract infections” or “severe respiratory tract infections cause development of asthma”).

5. Chapter 5: The Costs of Allergy and Asthma and the Potential Benefit of Prevention Strategies

Kevin B Weiss, Matthias Haus and Yoji Iikura

4.1. The costs of illness

Asthma and other allergic diseases represent chronic conditions that result in great social and economic impact on the affected persons and their families, health care systems, and society as whole. For example, the total costs of asthma vary from a low of \$433.5 million to a high of \$6.4 billion annually in Canada and the United States respectively. Other allergic diseases account for substantial economic burden as well. For example, in 1994, there were an estimated 39 million persons in the US suffering with allergic rhinitis accounting for an estimated \$1.2 billion in total costs.

In Australia, children lose approximately one million school days each year due to asthma. It is estimated that in the US, children account for over seven million days restricted to bed and ten million days missed from school each year. A child's asthma also affects family activities. Families with children who have asthma report that this illness influences a range of decisions concerning holidays, pets, furnishings, carpets, lifestyle, and household spending. To date, there is very little information on the economic impact for many countries with sizeable populations, such as India and Indonesia, and information for China is unavailable. However, based on epidemiological studies of allergy and asthma within such countries, it is likely that these conditions may account for substantial social and economic burden in these countries as well.

5.2. Building strategies for a health economic benefit of prevention of asthma and allergies

With substantive social and economic burden related to asthma and other allergic diseases, it is essential to

explore ways by which care for such individuals may be most effectively managed. While the literature that directly examines either the cost-effectiveness or cost-benefit of primary or secondary prevention for asthma and allergies is currently very limited, this literature suggests ways in which prevention may eventually lead to the most effective use of scarce health care resources. Strategies for reductions in allergen load at home, work, and in the environment are prime candidates. A recent US Institute of Medicine Report suggested that targeting reductions in smoking exposure and environmental exposure to house dust mites may be important, leading to effective reduction of the social and economic burden of asthma and allergies through prevention.

5.3. Policy implications of the economic burden of asthma and rhinitis

In order to reduce the global burden of asthma and other allergic conditions it will be necessary to identify the degree of community-specific disease burden, and design and test prevention strategies for their relative cost-effectiveness. Additionally the costs and benefits of introducing new strategies for prevention of asthma and allergy must be considered, not only in regards to cultural appropriateness, but also in light of the existing resources of each community.

5.4. Conclusions

Asthma and allergic diseases represent health conditions from which millions suffer physical impairments, reductions in quality of life, and economic impact. It is very conceivable that early prevention will lead to more effective use of healthcare resources.

5.5. Recommendations

There is a great need for health economic studies of various prevention strategies. While waiting for the funding and implementation of health economic evalua-

tions in this area, health economic modelling represents the most useful immediate strategy to explore the potential of prevention on reducing the economic and social burden from these diseases.

6. Chapter 6: Education

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6.1. Burden of asthma and allergy

Asthma is the most common chronic childhood illness, with an incidence of 10–15% in the paediatric population. Though it is also one of the most treatable and well-understood chronic conditions of childhood, it continues to increase in both prevalence and morbidity. Children with asthma miss school more frequently than healthy children and make more visits to emergency departments and physicians' offices. Children with asthma are major consumers of health services. In the USA an average of 6.4% of the annual family income of middle class families, and of 10% in low-income families, is spent for the management of childhood asthma.

6.2. Why do doctors underdiagnose and undertreat asthma and allergy?

Many doctors and health providers do not have sufficient updated information about the changing concept of asthma and allergy management and the new drugs available, leading to under-diagnosis and under-treatment. More importantly, in asthma treatment health providers do not have sufficient skill in operating the new inhalers and spacers, leading to poor patient skills and low compliance. Physicians also tend to overestimate patient compliance, and may fear its assessment as an audit of their clinical skills.

6.3. Why are patients not adhering to therapy?

In the absence of proper patient education, patients are often unaware that they have asthma and allergic disorders, and that it is possible to overcome these diseases and conduct a normal life. They remain unprotected from exposure to known allergens, ignore warning signs of attacks, incorrectly evaluate the severity of their disease, and either fail to take prescribed medications, or do so incorrectly. There is also a tendency for parents to underestimate the severity of their child's allergy, and particularly of individual

asthma attacks, even when fatal. Acknowledgment of all these factors is important in the planning of new health education programmes.

6.4. The importance of physician-patient partnerships

Traditionally, physician education has been disease-oriented rather than patient-oriented. More and more professionals are acknowledging however, that for care to be more effective there needs to be a partnership between the physician and the patient and his/her family. Patients want to play a role in the management process: they want to be informed on the one hand and to be decision-makers on the other. This mandates an educational dialogue based on open communication.

6.5. The effectiveness and cost-effectiveness of patient education programmes

Examples of asthma programmes are given below, and similar approaches must be taken for allergy. Patient education programmes have been shown to decrease the number of asthma attacks, reduce the severity of asthma symptoms and wheezing, decrease the number of wheezing episodes, and reduce the number of hospitalisations and hospitalisation days.

Studies have shown that education programmes increase patient knowledge about asthma, improve asthma self-management skills, and lead to better school attendance and performance. Furthermore, asthma education programmes induce better control of asthma symptoms, improve results on lung function tests, yield psychological benefits for patients and parents and upgrade the quality of life. Educational programmes are usually more effective when offered to asthmatic patients with high morbidity, and to low-income populations. Education programmes are cost-effective, because possible increases in drug use by patients, and in the number of primary physician visits per patient, are outweighed by the reduction in

emergency department visits and hospitalisations. Education on correct operation of the new inhalers and spacers should help to improve compliance.

6.6. What should an effective programme include?

The objective of the ideal asthma and allergy education programme is to improve self-management skills for both prevention and treatment, and to help families in decision making while encouraging them to work closely with the physician to resolve management problems. The programme should teach patients to recognise known triggers of disease, the signs and symptoms of attacks, the signs of worsening disease, and side effects of treatment. The patient should learn thereafter to correctly administer the prescribed medications, to normalise social activities, to effectively communicate with the physician and other health care personnel, and to apply co-management skills. Studies have shown that simple information programmes are insufficient, and the most effective programmes are those that integrate asthma and allergy care with behavioural theories. Each individual education programme must be modified to suit specific cultural, religious, educational, psychological, and economic factors, as well as the health beliefs and attitudes of the specific target population. Advanced technologies, such as videotapes, computer games, interactive computer programmes, and mass media campaigns should also be part of the learning process.

6.7. Who should be educated?

Asthma and allergy education programmes should be addressed to children, their families, and school personnel, and be accompanied by the education of the relevant medical professionals, namely medical

students, residents, and family physicians, as well as nurses, physiotherapists, pharmacists, and other ancillary medical staff.

6.8. Practical recommendations

Many national education programmes have been applied successfully and their results documented. However, in order to combine their benefits, establish uniform standards, and make these programmes available to all countries worldwide, a major international effort is essential. The various IAACI-WAO and WHO collaborative projects are excellent examples.

It might be of interest to consider defining an “Asthma and Allergy Prevention Promoting Country” that could include, for example:

- establishment by the country of a national interdisciplinary coalition on asthma and allergy prevention and education promotion, including representatives from all medical sectors
- allocation of government and private funds to prevention
- introduction of educational activities for medical personnel and establishment of an organisation for patient support with an emphasis on minority groups
- application of international evaluation tools, such as the ISAAC (International Study of Asthma and Allergies in Childhood), for comparing longitudinal studies in various populations, and participation in international initiatives and educational programs such as “World Allergy Awareness Day”, GLORIA (Global Recommendations in Allergy), and others
- co-operation of governmental offices in environmental control; and the publication of an annual national report on asthma and allergy status

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